the PTO-1449 Form and the applicants assume the Examiner has considered all the references stated therein. Return of a further initialed copy however is requested to confirm the same.

The specification has been amended to include the Abstract of the published application WO 99/32516, as originally filed with the application, on a separate sheet attached hereto.

The specification has been amended to include a description of Figure 1, as required on page 3 of Paper No. 14.

The certified copy of the priority document was filed January 29, 2002 and acknowledgement of the same in the Examiner's next communication is requested. See, attached copy of the undersigned's Submission of January 29, 2002 and the undersigned's postcard receipt indicating the Patent Office acknowledged receipt of the Submission and attachment.

Claim 3 has been amended in line 2, as requested by the Examiner in paragraph 10 of Paper No. 14. The Examiner's comment with regard to claim 3 in paragraph 11 of Paper No. 14 however is unclear as the noted "o" on line 2 is not found and clarification is requested in the event further amendments are required. Claim 5 has been amended to correct an inadvertent typographical error.

Claim 1 has been amended in response to the Examiner's rejection of claims 1-5 under Section 112, second paragraph, noted in paragraphs 13 and 14 of Paper No. 14. The Examiner is requested to indicate what aspect of the amended claims are unclear in the event the rejection is maintained. The applicants submit that one of ordinary skill

in the art would appreciate the metes and bounds of the claimed invention and further amendments should not be required.

The Section 112, first paragraph, rejection of claims 1-5 noted in paragraph 16 of Paper No. 14 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner will appreciate that claims 1-3 of the present application recite the following:

Claim 1. Orally, parenterally, trarisdermally or subcutaneously administrable pharmaceutical composition containing, as active ingredient, the amino acid sequence of the long pentraxin PTX3, and a pharmacologically acceptable excipient.

Claim 2. Composition according to claim 1, in which the sequence of the long pentraxin PTX3 is the sequence of naturally occurring PTX3.

Claim 3. Composition according to claim 2, in which the sequence of the long pentraxin PTX3 is the sequence of human PTX3.

On page 8 lines 14-15, the present application describes the following: *"PTX3 in 0.5% carboxymethylcellulose"*.

The Merck Index, Eleventh Edition, in the last two lines of page 278, point 1835, herewith enclosed, for the "Use" of carboxymethylcellulose reports: "**Pharmaceutical aid (suspending agent; tablet excipient; viscosity-increasing** agent)" (emphasis added).

It is evident for one of ordinary skill in the art that carboxymethylcellulose is an excipient useful for preparing a pharmaceutical composition comprising

PTX3.

For these reasons pharmaceutical compositions comprising PTX3 and an excipient, as claimed in claims 1-3, are supported by the text of the present application as filed, and the Section 112, first paragraph rejection should, accordingly, be withdrawn.

Moreover, on page 2 lines 1-23 and page 3 lines 1-5 of the present application, it is reported: "*PTX3 consists of two structural domains, an N-terminal unrelated to any known molecule, and a C-terminal similar to the short pentraxins such as C-reactive protein (CRP). A substantial degree of similarity has been found between human PTX3 (hPTX3) and animal PTX3s.*

The PTX3 gene is *located on chromosome 3 of the mouse in a region similar to the human 3q region (q24-28), in agreement with the documented location of hPTX3 in the 3q 25 region. Furthermore, mouse PTX3 (mPTX3) ... is very similar to hPTX3 in terms of organisation, location and sequence*

In particular, the degree of ***identity between the sequences is 82% between the human and mouse gene and reaches 90% if conservative substitutions are considered.***

The high degree of similarity between the hPTX3 and mPTX3 sequences is a sign of the high degree of conservation of pentraxin during evolution. "

(Emphasis added).

The degree of identity between the sequences of hPTX3 and mPTX3 and the high degree of similarity between their sequences is compelling evidence of the high degree

of conservation of pentraxin during evolution and that human pentraxin and mouse pentraxin would be expected to demonstrate similar pharmacological activity.

For these reasons, the Section 112, first paragraph rejection should be withdrawn.

While not believed necessary, the applicants request the Examiner's consideration of the following, further evidence of the ability of human PTX3 to provide a protective effect against infectious microbes, and specifically on the activity of pulmonary Aspergillosis

The Examiner will appreciate that it is known that *A. fumigatus* is a major human opportunistic pathogen under conditions of defective immunity and poses a formidable challenge to therapy. The following experiment demonstrate the function of PTX3 in resistance against *A. fumigatus* infection, in mice. The human PTX3 used was obtained as described in the present application.

PTX3 bound to *A. fumigatus* conidia

Among microbes recognized by PTX3, *Aspergillus fumigatus* is one important pathogen in immunodeficient individuals and pattern recognition receptors playing a nonredundant role *in vivo* against fungal infections of mammals have not been previously described. As shown in the following Fig. 1, PTX3 was found to bind to viable or heat inactivated *A. fumigatus* conidia as assessed using biotin labeled PTX3 or anti-PTX3 mAb and FACS, with an apparent Kd of 7.8×10^{-7}M. In contrast, no binding to *A. fumigatus* hyphae was observed (not shown). Similarly, PTX3 did not bind to the unrelated fungus *Candida albicans* (Fig. 1)

R le of PTX3 in resist nce to invasive pulmonary aspergillosis

As PTX3 bound *A. fuinigatus* conidia *in vitro,* a potential role for PTX3 in resistance in a murine model of invasive pulmonary aspergillosis was investigated. PTX3 -/- and +/+ mice were challenged with 2 x 10^8 spores of *A. fumigatus* intratracheally. Mice were monitored for mortality, fungal load and pathology in the organs. As shown in Table 1, wild type mice generally survive A *fumgatus* in this model of infection. In contrast, in two different experiments performed, PTX3 -/- mice showed a MST of 3 days and a survival rate of 0%. *A. fumigatus* invasiveness was also assessed as fungal burden in lungs and brain. As shown in Table 1 the increased susceptibility of PTX3 -/- mice correlated with a dramatic increase in lung colonization at day three of infection, with a 1000-fold increase in lung CFU in PTX3 *-/-* mice. The brain was not colonized in wild type mice, while in PTX3 *-/-* mice fungal burden in the brain was high (10^5 - 2 x 10^5 CFU/brain).

Mortality rate, MST and fungal burden in PTX3 *-/-* were equivalent to or worse than those obtained in PTX3 *+/+* mice after depletion of polymorphonuclear cells by treatment with anti-Gr-I (RB6.8C5) (Table 1).

In two *in vivo* experiments, PTX3 -/- mice were treated with 20-50 µg of purified hPTX3 intratracheally at the time of challenge (day 0) and intravenously or intraperitoneally (day 1 and 2). As shown in Table 1, in both cases, the phenotype was reverted and treated PTX3 -/- mice behaved as PTX3 +/+ mice: mortality rate was reverted to 0/4 and 1/4, respectively and MST was more than 60 days as in PTX3 *+/+* mice. Lung burden was reduced 2-4-fold by treatment. The restoration of resistance to invasive pulmonary aspergillosis (IPA) in PTX3 *-/-* mice by PTX3 administration

confirms the critical and specific role of PTX3 in this fungal infection.

PTX3 improve Phagocytosis of A fumigatus conidia by alveolar macrophages an in vitro internalization assay.

The ability of alveolar macrophages to ingest resting conidia in vitro, was significantly impaired in PTX3 -/- mice, as compared to PTX3 +/+ mice. However, PTX3 restored the phagocytic activities of cells from PTX3 -/- mice and, to a lesser extent, potentiated those of PTX3 +/+ mice (Fig. 2 in the following). This phagocytosis assay on PTX +/+ macrophages confirms a therapeutic use of PTX3 for treatment of pulmonary aspergillosis.

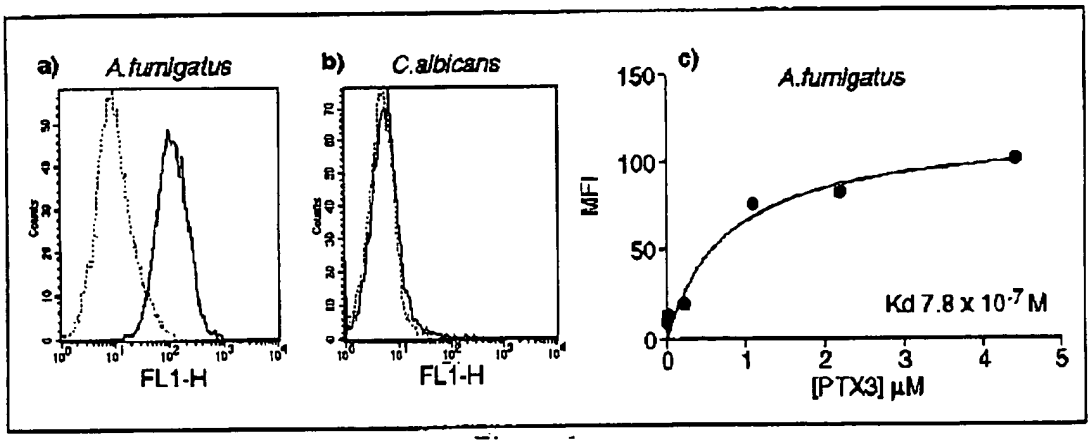
TABLE. 1

Susceptibility of PTX3 -/- mice to invasive pulmonary aspergillosis

Mice (a)	Treatment (days)	MST (b)	Dead/total (c)	Brain CFU (c)	Lung CFU
Exp. 1					
PTX3 +/+	None	>60	0/3	0	8100
PTX3 +/+	RB6-8C5	4	4/4	34800	170100
PTX3 -/-	None	3	3/3	142200	706500
PTX3 -/-	RB6-8C5	3	3/3	187200	603750
Exp. 2					
PTX3 +/+	None	>60	0/6	ND	12900
PTX3 -/-	None	3	7/7	ND	233250
PTX3 -/-	PTX3*	>60	0/4	ND	60900
PTX3 -/-	PTX3§	>60	1/4	ND	101700
Exp. 3					
C57B1/6	None	>60	0/10	0	1800
C1q -/-	None	2	6/10	450	400000

Mice were infected intratracheally with *A.fumigatus* conidia (2 x 10^8/mouse) on day 0. (a) Mice were treated with *RB6-8C5* monoclonal antibody (100 µg/mouse) intraperitoneally 2 h before fungal challenge to obtain PMN depletion or with 20 (*) or 50 *(§)*µg PTX3 intratracheally on day 0 and intravenously on day 1 and 2. (b) MST: median survival time. (c) CFU were determined at day 3 after infection.

Figure 1



Binding of PTX3 to *A.fumigatus* conidia. FACS analysis of PTX3 binding to a) *A.fumigatus* and b) *C. albicans* conidia. Binding was revealed by biotinylated PTX3 followed by FITC-labeled streptavidin. The right panel c) shows the specific binding of PTX3 to *A.fumigatus* conidia. Binding is saturable with a Kd of 7.4 x 10^{-8}M (assuming for PTX3 the mass of the protomer, 45 kDa).

Figure 2

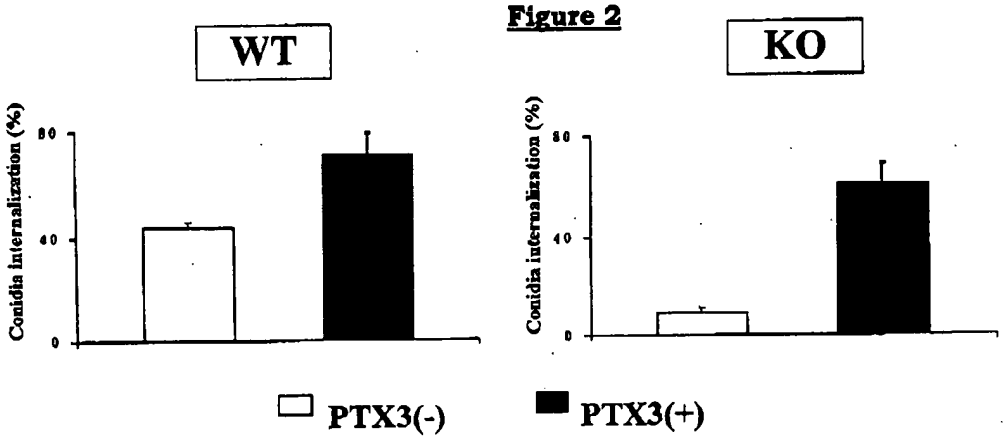


Figure 2: Alveolar macrophages isolated from the indicated mice (2 x 10^5 cells/200 µl) obtained by plastic adherence from the bronchoalveolar lavage fluid, were incubated at 37° C for 2h with 10^6 conidia in 6 ml polypropylene tubes (N. 2063, Falcon), in 200 µl of Iscove medium containing 5 µg/ml polymixin B (Sigma) and 50 µg/ml gentamycin but no FCS to avoid non specific activation by serum components. Phagocytic cells were separated from non phagocytosed *A fumigatus* cells by centrifugation on a fetal serum gradient. Harvest phagocytic cells was used for cytospin preparation. After Diff Quik

staining fungal cell internalization was expressed according to the following formula: Conidia internalization = number of cell containing one or more fungal cells / 100 cells: In PTX3 (+), 20 µg/ml PTX3 was added.

The claims are therefore submitted to be supported by an enabling disclosure and withdrawal of the Section 112 rejection of claims 1-5 is requested.

The Section 112, first paragraph, rejection of claims 1-5 noted in paragraph 17 of Paper No. 14 is traversed. Reconsideration and withdrawal of the rejection are rejected in view of the following comments.

As noted above, claims 1-3 of the present application recite:

Claim 1. Orally, parenterally, transdermally or subcutaneously administrable pharmaceutical composition containing, as active ingredient, the amino acid sequence of the long pentraxin PTX3, and a pharmacologically acceptable excipient.

Claim 2. Composition according to claim I, in which the sequence of the long pentraxin PTX3 is the sequence of naturally occurring PTX3.

Claim 3. Composition according to claim 2, in which the sequence of the long pentraxin PTX3 is the sequence of human PTX3.

On page 8 lines 14-15 of the present application is reported: *"PTX3 in 0.5% carboxymethylcellulose".*

The Merck Index, Eleventh Edition, in the last two lines of page 278, point 1835, herewith enclosed, for the "Use" of carboxymethylcellulose reports: **"Pharmaceutical aid (suspending agent; tablet excipient; viscosity-increasing agent)"(emphasis added).**

It is evident for one of ordinary skill in the art that carboxymethylcellulose is an

excipient useful for preparing a pharmaceutical composition comprising PTX3.

For these reasons pharmaceutical compositions comprising PTX3 and an excipient, as claimed in claims 1-3, are supported by the text of the present application as filed, and this rejection should be withdrawn.

Moreover, as above mentioned, it certainly may be correct, as pointed out by the Examiner, that minor changes in primary sequence can result in dramatic alterations in structure and function.

However, as noted above *the degree of* ***identity between the sequences is 82% between the human and mouse gene and reaches 90% if conservative substitutions are considered. The high degree of similarity between the hPTX3 and mPTX3 sequences is a sign of the high degree of conservation of pentraxin during evolution.***

For these reasons the applicants believe the Section 112, first paragraph "written description", rejection should be withdrawn.

The Section 102 rejection of claims 1-5 over Alles (Blood, 1994 84 (10): 3483-3493), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner alleges that Alles et al. teach a composition comprising a naturally occurring human PTX3 from human peripheral blood mononuclear cells and a pharmacologically acceptable excipient injected subcutaneously into an animal (see page 3484 and 3485 regarding the production of antibodies).

Claims 1-5 of the present application relates to a **pharmac utical** composition

containing, as active ingredient, the amino acid sequence of the long pentraxin PTX3 and a pharmacologically acceptable excipient, in which the sequence of the long pentraxin PTX3 is, for example, the sequence of human PTX3, for the treatment of infectious and inflammatory diseases or tumours, in which the infectious disease is caused by bacteria, fungi, protozoa or viruses.

Alles et al. on page 3484 and 3485 teaches the production of antibodies to PTX3 and reports: "Immunization of rabbits to obtain anti-PTX3 antibody was performed by repeated subcutaneous (SC) injection with the recombinant protein produced in BL21 (DE3) bacteria. Briefly, a 1,222-bp fragment of PTX3 (from nucleotide 36 to nucleotide 1258 according to our published sequence)[1] was subcloned into the *Bam*HI site of pETc vector[46] and used to transform competent BL21 cells[46]. Colonies were expanded in NZCYM medium for 4 to 5 hours at 37°C and then induced with 0.6 mmol/LIPTG (Sigma) for 3 hours. At the end of the incubation the bacteria were pelleted, dissolved in sonication buffer ... sonicated for 10 minutes on ice, and then ultracentrifuged at 35,000 rpm for 30 minutes. The sonication and ultracentrifugation steps were repeated twice and the pellets were dissolved in 8 mol/ L urea.

The solubilized proteins were separated in a 10% polyacrlamide gel under reducing conditions. The gel slice containing recombinant PTX3 was excised, mechanically disrupted in saline, and injected SC into a 28-day-old rabbit ..... Boosts were administered at 2, 4, and 9 weeks and serum was collected 7 days after the last injection" (Emphasis added).

It will be appreciated by one of ordinary skill in the art that the **solubilized**

proteins separated in a 10% polyacrilamide gel under reducing conditions, and **the gel slice excised, containing recombinant PTX3** which was mechanically disrupted in saline, **is not a pharmaceutical composition and is rather a toxic composition** injected into rabbits for producing antibodies. In fact, the applicants believe that one of ordinary skill well knows that the gel slice excised, containing recombinant PTX3 contains also polyacrilamide and that polyacrilamide is neurotoxic and cannot be present in a pharmaceutical composition for human use.

Therefore, the solution described by Alles is not a pharmaceutical composition. As the cited art fails to teach each and every aspect of the presently claimed invention, the Section 102 rejection should be withdrawn.

In view of the above, and attached, the claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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MARKED UP CLAIMS

1. (Amended) Orally, parenterally, transdermally or subcutaneously administrable pharmaceutical composition containing, as active ingredient, the amino acid sequence of the long pentraxin PTX3, and a pharmacologically acceptable excipient.

3. (Amended) Composition according to claim 2, in which the sequence of the long pentraxin [FITX3] PTX3 is the sequence of human PTX3.

5. (Amended) Composition according to claim 4, for the treatment of diseases caused by bacteria, fungi, protozoa [o] or viruses.

C#/M#: 2801-18
Atty: Arthur R. Crawford
Date: January 29, 2002

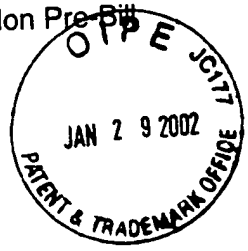
Serial No.: 09/555,473
Inventor/s: BOTTAZZI et al.

Title: PHARMACEUTICAL COMPOSITIONS CONTAINING THE LONG PENTRAXIN PTX3

XX **Priority document/s**

$ Fee (Check) - **Pre-Bill**

$ Fee (Check) - Non Pre-Bill



$0.00 **Total Fee Enclosed**

Other:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

BOTTAZZI et al.

Serial No. 09/555,473

Filed: May 31, 2000

Atty. Ref.: 2801-18

Group: 1644

Examiner: Jamroz

For: PHARMACEUTICAL COMPOSITIONS CONTAINING THE LONG PENTRAXIN PTX3

* * * * * * * * * * *

January 29, 2002

Assistant Commissioner for Patents
Washington, DC 20231

SUBMISSION OF PRIORITY DOCUMENTS

Sir:

It is respectfully requested that this application be given the benefit of the foreign filing date under the provisions of 35 U.S.C. §119 of the following, a certified copy of which is submitted herewith:

Application No.	Country of Origin	Filed
RM97 A000796	Italy	December 19, 1997

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

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INFORMATION DISCLOSURE CITATION

ATTY. DOCKET NO.: 2801-18

SERIAL NO.: (To be assigned)

APPLICANT: BOTTAZZI et al.

(Use several sheets if necessary)

FILING DATE: May 31, 2000

GROUP:

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
MJ		93 21313 A	10/1993	WO				

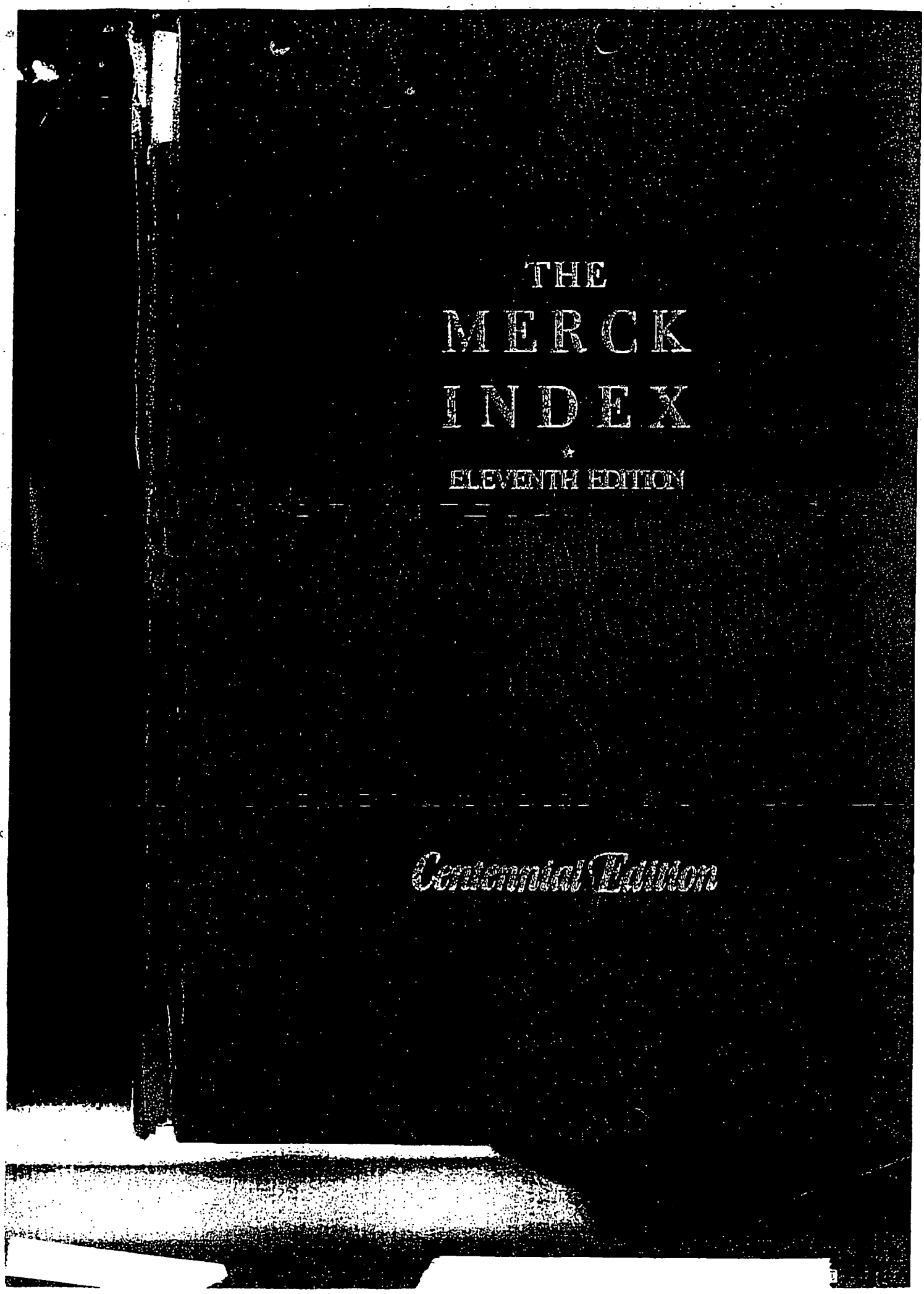
OTHER DOCUMENTS (including Author, Title, Date, Pertinent pages, etc.)

MJ		BOTTAZZI, B. (1) et al.: "Preliminary biochemical and biological characterization of ptx3, a new member of the pentraxin gene family." CYTOKINE, (11/1997) vol. 9, no. 11, pp. 903. Meeting Info.: Fifth Annual Conference of the International Cytokine Society Lake Tahoe, Nevada, USA 11/1997 International Cytokine Society
↓		INTRONA M et al.: "Cloning of mouse ptx3 a new member of the pentraxin gene family expressed at extrahepatic sites." Blook, (3/1996) 87 (5) 1862-72.
		VOURET-CRAVIARI V et al.: "Expression of a long pentraxin, PTX3, by monocytes exposed to the mycobacterial cell wall component lipoarabinomannan." Infection and Immunity, 4/1997) 65 (4) 1345-50

Examiner*: M.E. Gamion | Date Considered: 4/19/02

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

Form PTO-FB-A820 (Also PTO-1449)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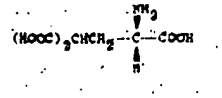
Centennial Edition



Crystals, mp 167-167.5° (dec). $[\alpha]_D^{25}$ +35.3° (c = 1 in 6N HCl).

DL-Form, white powder, mp 90-92°.

1835. Carboxymethylcellulose Sodium. *Carboxymethyl ether cellulose sodium salt;* CMC; sodium carboxymethylcellulose; sodium cellulose glycolate; Carmethose; Cel-O-Brandt; Cethylose; Glykocellon; Carbose D; Thylose; Xylo-Mucine; Tylose MGA; Cellolax; Polycell. R_xOCH_2COONa. Prepd by treating alkali cellulose with sodium chloroacetate; Faith, Keyes & Clark's *Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 235-238. Review and bibliography: Ott, *Cellulose and Cellulose Derivatives*, New York, 1946 (2nd ed., 1955).

White granules. Soly in water depends on degree of substitution. Water-soluble CMC is available in various viscosities (5-2000 centipoises in 1% soln), and the soly is equally good in hot and cold water (difference from methyl cellulose). Also the presence of metal salts has little effect on the viscosity. Solns are stable between pH 2 and 10. Below pH 2 precipitation of a solid occurs, above pH 10 the viscosity decreases rapidly. pKa 4.30. The free acid is obtained from aq soln at pH 2.5 and may be precipitated with alcohol.

USE: In drilling muds, in detergents as a soil-suspending agent, in resin emulsion paints, adhesives, printing inks, textile sizes, as protective colloid in general. As stabilizer in foods. Pharmaceutic aid (suspending agent; tablet excipient; viscosity-increasing agent).

1836. Carboxypolymethylene. *Carbomer; carbopol;* carboxyvinyl polymer. A vinyl polymer with active carboxyl groups. Description: *Chem. & Eng. News* 36, 64 (Sept. 29, 1958).

White powder. Highly ionic and slightly acidic. Reacts with fatty amines to form thick and stable emulsions of oils in water.

USE: Thickening, suspending, dispersing, emulsifying agent. In the cosmetic and textile printing fields, in printing inks, in emulsion-based lubricants, in pharmaceuticals, polishes, waxes, paints, waterproof and oil-proof coatings, in industrial specialties.

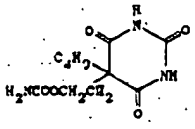
1837. Carbromal. *N-(Aminocarbonyl)-2-bromo-2-ethylbutanamide;* (α-bromo-α-ethylbutyryl)urea; (α-bromo-α-ethylbutyryl)carbamide; bromodiethylacetylurea; bromodiethylacetylcarbamide; Tildin; Adalin; Planadalin; Diacid; Addisomnol; Bromadal; Uradal; Nyctal. $C_7H_{13}BrN_2O_2$; mol wt 237.11. C 35.46%, H 5.53%, Br 33.70%, N 11.82%, O 13.50%. $(C_2H_5)_2CBrCONHCONH_2$. Prepd by heating urea (to ~50°) with α-bromo-α-ethylbutyryl bromide $(C_2H_5)_2CBrCOBr$, *see* Ger. pat. 228,710 (1910); *Frdl.* 10, 1160; *Chem. Zentr.* 1910, II, 1008. Large patent literature tabulated in Slotta, *Grundriss der modernen Arzneistoff-Synthese* (Stuttgart, 1931); H. P. Kaufmann, *Arzneimittel-Synthese* (Berlin, 1953).

Crystals, mp 116-119°. One gram dissolves in about 3000 ml water, 18 ml alcohol, 3 ml chloroform, 14 ml ether. It is very sol in boiling alcohol and dissolves in cooled sulfuric, nitric and hydrochloric acids, from which it is precipitated on dilution with water. It is dissolved by solns of alkali hydroxides. LD orally in dogs: 450 mg/kg, *Handbook of Toxicology* vol. 1, W. S. Spector, Ed. (Saunders, Philadelphia, 1956) pp 14-15.

Caution: This substance may be habit forming and is listed in the U.S. Code of Federal Regulations, Title 21 Part 329.1 (1987).

THERAP CAT: Sedative, hypnotic.

1838. Carbubarb. *5-[2-[(Aminocarbonyl)oxy]ethyl]-5-butyl-2,4,6(1H,3H,3H)-pyrimidinetrione; carbamic acid ester with 5-butyl-5-(2-hydroxyethyl)barbituric acid;* 5-butyl-5-carbamoyloxyethylbarbituric acid; 5-butyl-5-(2-hydroxyethyl)barbituric acid carbamate; carbamic acid ester with 5-(β-hydroxyethyl)-5-butylmalonylurea; 5-(β-hydroxyethyl)-5-butylmalonylurea carbamate; Nogexan. $C_{11}H_{17}N_3O_5$; mol wt 271.27. C 48.70%, H 6.32%, N 15.49%, O 29.49%. Prepn: Fr. pat. M1059 (1962 to Consortium Mondial des Grandes Marques). *C.A.* 59, 7539c (1963); Buzas, U.S. pat. 3,150,137 (1964). Purification and toxicity: Fr. pat. M2633 (1964 to Interco Fribourg). *C.A.* 62, 1671e (1965).

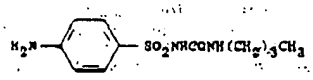


Crystals from ethanol, mp 192-194°. LD_{50} s.c. in mice: 1.4 g/kg (Fr. pat. M2633).

Note: This is a controlled substance (depressant) listed in the U.S. Code of Federal Regulations, Title 21 Part 1308.13 (1987).

THERAP CAT: Sedative, hypnotic.

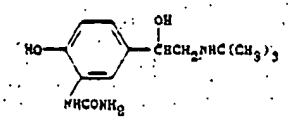
1839. Carbutamide. *4-Amino-N-[(butylamino)carbonyl]benzenesulfonamide; 1-butyl-3-sulfanilylurea; N1-(butylcarbamoyl)sulfanilamide; N1-sulfanilyl-N2-butylurea; N1-sulfanilyl-N2-butylcarbamide; N-(4-aminobenzenesulfonyl)-N'-butylurea;* aminophenylurobutane; BZ 55; U 6987; Nadisan; Invenol; Emedan; Oranil; Orasulin; Glucofren; Bukarban; Bucarban; Cicloral; Glucidoral; Alentin; Norboral; Bucrol. $C_{11}H_{17}N_3O_3S$; mol wt 271.35. C 48.69%, H 6.32%, N 15.49%, O 17.69%, S 11.82%. *Ref:* Achelis, Hardebeck, *Dsch. Med. Wochenschr.* 80, 1452 (1955); Achelis *et al., Arch. Exp. Pathol. Pharmakol.* 228, 163 (1956). Prepn from butylurea and sulfanilamide: Samaniego, Span. pat. 229,696 (1956). *C.A.* 51, 7413 (1957); E. Haack, A. Hagedorn, U.S. pat. 2,907,692 (1959 to Boehringer, Mann.).



Crystals, mp 144-145°. Sol in water at pH 5 to 8. LD_{50} s.c. in mice: 3 g/kg (Haack, Hagedorn).

THERAP CAT: Antidiabetic.

1840. Carbuterol. *[5-[2-[(1,1-Dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxyphenyl]urea;* α-(t-butylaminomethyl)-4-hydroxy-3-ureidobenzyl alcohol. $C_{13}H_{21}N_3O_3$; mol wt 267.33. C 58.41%, H 7.92%, N 15.71%, O 17.96%. A β-adrenergic agonist related to isoproterenol, q.v., with selectivity for airway smooth muscle receptors. Prepn: C. Kaiser, S. T. Ross, Ger. pat. 2,106,620 corresp to U.S. pat. 3,763,232 (1971, 1973 both to SKF); C. Kaiser *et al., J. Med. Chem.* 17, 49 (1974). Pharmacology, mechanism of action, toxicity study: J. R. Wardell *et al., J. Pharmacol. Exp. Ther.* 189, 167 (1974). Analysis in aq soln: L. J. Ravin *et al., J. Pharm. Sci.* 67, 1523 (1978). Clinical study: T. D. James, H. A. Lyons, *J. Am. Med. Assoc.* 241, 704 (1979).



Cryst, mp 174-176°. LD_{50} in mice: 32.8 mg/kg i.v.; 3134.6 mg/kg orally; in rats: 77.2 mg/kg i.v., J. R. Wardell *et al., loc. cit.*

Hydrochloride. $C_{13}H_{22}ClN_3O_3$, *SKF 40383, Bronsecur, Pirem.* Cryst from ethanol/ether, mp 205-207° (dec).

THERAP CAT: Bronchodilator.

1841. Cardamom Seed. Grains of paradise. Dried ripe seeds of *Elettaria cardamomum* Maton, *Zingiberaceae. Habit:* Malabar, cultivated in India, Ceylon, Guatemala. *Constit:* Resin; 2-8% essential oil, 1-2% fixed oil. The essential oil contains eucalyptol (cineol), sabinene, *d*,α-terpineol and acetate, borneol, limonene, terpinene, 1-terpinen-4-ol and its formate and acetate. The fixed oil consists of the